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EXAMINER
GIBBS, TERRA C

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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/774,809	Applicant(s) MCKAY ET AL.	
	Examiner Terra Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-33 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-33 are pending in the instant application.

Specification

The references to the American Type Culture Collection found in the instant specification at page 64, lines 14-15 and page 102, lines 4-5 must include a *current* and *complete* address, including street address. For example, on page 64, the address reads, "American Type Culture Collection, Rockville, MD" and on page 102 reads, "American Type Culture Collection, Richmond, VA".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U. S. Patent No. 6,221,850, claims 1-2 of U.S. Patent No. 5,877,309 and claims 1-3 of U.S. Patent No. 6,133,246. Although the conflicting claims are not identical, they are not patentably distinct from each other because: Oligonucleotides of claims 1-9, 18-20 and 25 of the instant invention embrace the embodiments

of claims 1-10, 19-20 and 23 of '850; pharmaceutical compositions of claims 10-12 of the instant invention embrace the embodiments of claims 11-13 of '850; specific embodiments of claims 13-17 and 21-24 of the instant invention overlap with the embodiments of claims 14-18 and 21-22 of 850. Oligonucleotides of claims 1 and 9 of the instant invention embrace the embodiments of claims 1-2 of '309. Specific embodiments of claims 23, 24-25 and 28 of the instant invention overlap with claims 1-3 of '246.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-33 are broadly drawn to oligonucleotides comprising 8 to 30 nucleotides wherein said nucleotide consist of a sequence specifically hybridizable to a nucleic acid encoding a JNK protein and specifically hybridizable under the condition of modulating the expression of said JNK protein, and modified oligonucleotides and pharmaceutical compositions thereof; wherein the JNK protein is that of a mammal; and wherein said oligonucleotides are specifically hybridizable with a nucleic acid encoding a first isoform but not a second isoform, or wherein said oligonucleotides are specifically hybridizable to two or more nucleic acids encoding different isoforms of JNK protein. The specification discloses at page 15, lines 30-34

the terminology "specifically hybridizable" as indicating "a sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target." The specification at page 16, lines 17-27, discloses that an "oligonucleotide need not be 100% complementary to its target DNA sequence to be specifically hybridizable" and contemplates specific hybridization "under physiological conditions in the case of *in vivo* assays or therapeutic treatment, or in the case of *in vitro* assays, under conditions in which the assays are performed."

The specification contemplates specific hybridization to a nucleic acid that is not 100% complementary, but does not indicate how much less than 100% complementary is acceptable. Furthermore, the specification contemplates different hybridization conditions, and does not indicate the parameters of experimental conditions. See, also, the above rejection under 35 U.S.C. 112, second paragraph. Thus, applicant's disclosure combined with what was known in the art is not sufficient to describe the claimed genus of oligonucleotides that specifically hybridize a JNK protein, in such clear and concise and exact terms as to show applicants were in possession of the claimed invention.

The specification provides no particular guidance or direction for antisense oligonucleotide (ASON) of only 8 nucleotides in length, which is theoretically too short in length to uniquely target a specific gene. Applicants have not shown that any antisense oligonucleotides of only 8 nucleotides would have the specificity required for *in vivo* modulation of expression of a JNK-encoding gene. The specification does not provide guidance for the delivery of antisense oligonucleotides of only 8 nucleotides into target organs and cells in an animal in quantity sufficient to inhibit the expression of JNK protein. One of skill in the art would not be reasonably apprised of which oligonucleotides of the claimed invention would

specifically hybridize to nucleic acids encoding JNK protein. (*see. also*. rejections under 35 U.S.C. 112, second paragraph and first paragraph).

Branch (TIBS Vol. 23, February, 1998) at page 47, paragraph 6, teaches that an ASON of 10-nucleotide sequences may bind on average to 3000 sites in the human genome, so that ASON that are short in length are likely to bind to more than the target gene. Thus, even though a sequence may be a consensus sequence to several different effective ASON, a new ASON that consists of only that consensus sequence will bind to many non-target sites if the consensus sequence is too short in length. This unwanted binding of the short consensus ASON may reduce the quantity of ASON available to bind to the targeted mRNA.

The unpredictability of the art of antisense therapy in general further adds to the lack of enablement for the current invention. For example, the following references are cited herein to illustrate the state of unpredictability of the art of antisense treatment in organisms. Crooke (Antisense Research and Application: Basic Principles of Antisense Therapeutics, 1998, pages 1-50) teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1 which failed to demonstrate significant difference from placebo (BioWorld Today, 1999, Vol. 10:paragraphs 3 and 5-7 on page 1). It is clear from Branch and Crooke that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

In view of the unpredictability of the art, the quantity of experimentation required would include the design and manufacture of oligonucleotides of 8 nucleotides in length that specifically bind nucleic acids encoding any JNK protein of a representative number of species or mammals such that expression is modulated and overcoming the obstacle to routine antisense therapies as exemplified in the references discussed above. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Claims 13-17 and 21-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the expression of a JNK protein in cells *in vitro* (e.g. cells in culture) does not reasonably provide for a method of modulating the expression of a JNK protein in cells *in vivo* (e.g. whole animal). The specification does not enable any person or skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 13-17 and 21-33 are drawn to methods of modulating cell cycle progression in an animal and methods of treating an animal having a hyperproliferative disease.

The specification as filed shows *in vitro* modulation of JNK proteins and tumor growth rates of prostate cells after JNK2 antisense treatment.

The specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trail and error experimentation. The specification does not provide a meaningful nexus between modulating the expression of a JNK protein in cells *in vitro* to modulating the expression of a JNK protein in cells *in vivo*. It is unpredictable as to whether *in vitro* modulation of a JNK protein correlates to in modulation of a JNK protein *in vivo*.

The specification as filed contemplates an antisense oligonucleotide as a mode for modulation of a JNK protein *in vivo*. Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1998: Stanley T. Crooke, Basic Principles of Anitsense Therapeutics, Springer-Verlag, NY, p. 3. ,1998), states "extrapolations *from in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies."

It is clear from Crooke that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

It would appear that in view of the above, one of ordinary skill in the art would have to engage in undue trial and error experimentation to practice the instant invention. In view of the unpredictability of the art, the quantity of experimentation required would include the specific mode of delivery, intracellular target, variability in contact time and therapeutic efficacy that specifically modulate the expression of a JNK protein in cells *in vivo*... and overcoming the obstacles to routine antisense therapies as exemplified in the references discussed above. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 9, 14 and 20 are rejected under 35 U.S.C. 102(b) as anticipated by Seimiya et al. (Journal of Biological Chemistry, 1997 Vol. 272:4631-4636).

Claims 1, 9 and 20 are drawn to oligonucleotides comprising 8 to 30 nucleotides wherein said nucleotide consists of a sequence specifically hybridizable to a nucleic acid encoding a JNK protein and specifically hybridizable under the condition of modulating the expression of said JNK protein, and where the JNK protein is that of a mammal. Claim 14 is drawn to a method of modulating the expression of JNK cells in cells comprising contacting said cells with the oligonucleotide of claim 1.

Seimiya et al. disclose an oligonucleotide consisting of 24 nucleotides wherein said nucleotide is an antisense oligonucleotide specific for the JNK sense sequence (see page 4632, paragraph 9) and where the JNK protein is that of a mammal. Seimiya et al. disclose an anti-JNK oligonucleotide that decreases the amount of JNK protein in culture (see page 4634 paragraph 2 and Fig. 5) and a method of contacting this antisense oligonucleotide to modulate the expression of the JNK protein.

Claims 13 and 28-33 are rejected under 35 U.S.C. 102(b) as anticipated by Karin et al. [U.S. Patent No. 5837244].

Claims 13 and 28-33 are drawn to a method of treating an animal having a hyperproliferative disease comprising administering a prophylactically or therapeutically effective amount of a JNK oligonucleotide.

Karin et al. disclose a method of treating a cell proliferative disorder associated with JNK comprising administering to a subject with the disorder a therapeutically effective amount of reagent which modulates JNK (see column 12, lines 10-14 and claims #1-2). Karin et al. disclose the reagent is an antisense polynucleotide (see column 7, lines 21-39 and claim #2). Karin et al. further disclose antisense oligonucleotides of about 15 nucleotides are preferred, since they are easily synthesized (see column 8, lines 58-60). Karin et al. further disclose, for example, the method may be useful in treating malignancies of various organ systems, such as lung, prostate cancer, cell proliferative diseases and other types of acute inflammation (see column 12, lines 28-34).

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seimiya et al., Barachini et al. [U.S. Patent No. 5801154] Shibahara et al., (Nucleic Acids Research, 1989

Vol. 17:239-52), Kallunki et al. (Genes and Development, 1994 p 2996-3007) and Karin et al. [U.S. Patent No. 5837244].

Claims 2-8 and 19 are drawn to the antisense oligonucleotide of claim 1 wherein: At least one of the covalent linkages is modified; at least one of the nucleotides has a modified nucleobase; at least one of the nucleotides has a modified sugar moiety; at least one of the covalent linkages is modified and at least one of the nucleotides has a modified sugar moiety; at least two n-n-contiguous nucleotides have modified sugar moieties; at least two non-contiguous nucleotides have modified sugar moieties and at least of one the covalent linkages is modified; and at least one lipophilic moiety which enhances cellular uptake of the oligonucleotide and wherein the modified nucleobase is 5-methylcytosine, respectively. Claim 9 is drawn to an oligonucleotide comprising from 8-30 nucleotides connected by covalent linkages, wherein said oligonucleotide has a sequence specifically hybridizable with a nucleic acid encoding a first isoform of a JNK protein and is not specifically hybridizable with a nucleic acid encoding a second isoform of the JNK protein, so that the oligonucleotide modulates the expression of the first isoform of the JNK protein but does not modulate the expression of the second isoform of the JNK proteins.

Seimiya et al., teach oligonucleotides comprising 8 to 30 nucleotides wherein said nucleotide consists of a sequence specifically hybridizable to a nucleic acid encoding a JNK protein and specifically hybridizable under the condition of modulating the expression of said JNK protein , and where the JNK protein is that of a mammal. Claim 14 is drawn to a method of modulating the expression of JNK cells in cells comprising contacting said cells with the oligonucleotide of claim 1. *See* above rejection under 35 U.S.C. 102(b).

Seimiya et al. do not teach the antisense oligonucleotide of claim 1 wherein: At least one of the covalent linkages is modified; at least one of the nucleotides has a modified nucleobase: at least one of the nucleotides has a modified sugar moiety; at least one of the covalent linkages is modified and at least one of the nucleotides has a modified sugar moiety; at least two non-contiguous nucleotides have modified sugar moieties; at least two non-contiguous nucleotides have modified sugar moieties and at least of one the covalent linkages is modified; and at least one lipophilic moiety which enhances cellular uptake of the oligonucleotide and wherein the modified nucleobase is 5-methylcytosine, respectively. Seimiya et al., do not teach an antisense oligonucleotide which has a sequence specifically hybridizable with a nucleic acid encoding a first isoform of a JNK protein and is not specifically hybridizable with a nucleic acid encoding a second isoform of the JNK protein, so that the oligonucleotide modulates the expression of the first isoform of the JNK protein but does not modulate the expression of the second isoform of the JNK proteins.

Baracchini et al. teach at least one modified covalent linkage, (see page 7, lines 15-18), as in claim 2; at least one of the nucleotides with a modified nucleobase, (see page 7, lines 15-18), as in claim 3; at least one of the nucleotides has a modified sugar moiety, (see page 6, lines 58-59), as in claim 4; and at least one lipophilic moiety which enhances the cellular uptake of the oligonucleotide, (see page 7, lines 43-67), as in claim 8. Baracchini et al. teach oligonucleotides comprising 5-methylcytosine (see page 7, line 23).

Shibahara et al. teach at least two non-contiguous nucleotides having modified sugar moieties, (see page 245, Figure 1), as in claim 6; and at least two "non-contiguous" nucleotides having modified sugar moieties and at least one the modified covalent linkages, (see page 245, Figure 1), as in claim 7.

Kallunki et al., teach a nucleic acid encoding a first isoform of a JNK protein and which is not identical to a second isoform of the JNK protein, because of "a small region located next to the catalytic pocket of the [JNK] enzyme.

Baracchini et al., Shibahara et al., and Kallunki et al. do not teach a method of treating an animal having a hyperproliferative disease comprising administering a prophylactically or therapeutically effective amount of a JNK oligonucleotide.

Karin et al. teach a method of treating a cell proliferative disorder associated with JNK.

Karin et al. teach a method of treating a cell proliferative disorder associated with JNK comprising administering to a subject with the disorder a therapeutically effective amount of reagent which modulates JNK (see column 12, lines 10-14 and claims #1-2). Karin et al. teach the reagent is an antisense polynucleotide (see column 7, lines 21-39 and claim #2). Karin et al. further teach antisense oligonucleotides of about 15 nucleotides are preferred, since they are easily synthesized (see column 8, lines 58-60). Karin et al. further teach, for example, the method may be useful in treating malignancies of various organ systems, such as lung, prostate cancer, cell proliferative diseases and other types of acute inflammation (see column 12, lines 28-34).

It would have obvious at the time the invention was made to one of ordinary skill in the art to make the antisense oligonucleotide of claim 1, as taught by Seimiya et al., with the modified covalent linkages, nucleobases, sugar moieties and lipophilic moieties, as taught by Baracchini et al. and with at least two non-contiguous nucleotides having modified sugar moieties and at least one modified covalent linkages, as taught by Shibahara et al. Furthermore, one of ordinary skill in the art would have been motivated to make antisense oligonucleotides, as taught by Seimiya et al., with the different nucleotide sequences encoding separate JNK

isoforms, as taught by Kallunki et al., in order to produce an antisense oligonucleotide which has a sequence specifically hybridizable with a nucleic acid encoding a first isoform of a JNK protein and is not specifically hybridizable with a nucleic acid encoding a second isoform of the JNK protein, so that the oligonucleotide modulates the expression of the first isoform of the JNK protein but does not modulate the expression of the second isoform of the JNK proteins.

One of ordinary skill in the art also would have been motivated to make modified oligonucleotides since Baracchini et al. teach modified oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nuclease (see page 6, lines 27-31). Furthermore, one of ordinary skill in the art also would have been motivated to make antisense oligonucleotide that target specific JNK isoforms because the isoforms, "JNK2 displays considerably higher affinity toward c-Jun than JNK1 does", as taught by Kallunki et al., at page 2997, paragraph 1. Thus one of ordinary skill in the art would have been motivated to differentiate between the inhibition of expression of JNK2, which has a much higher affinity for the potential oncogene c-Jun, and JNK1, which might regulate other substrates that were part of the normal functioning of the cell, in order to minimize untoward side-effects of, for example, antisense cancer therapy. One of ordinary skill in the art would have had a reasonable expectation of success of making antisense oligonucleotides that target mammalian JNK-encoding nucleotide sequences, as taught by Seimiya et al., with the oligonucleotide modifications as taught by the reference of Baracchini et al. and Shibahara et al. One of ordinary skill in the art would have had a reasonable expectation of success to make antisense oligonucleotides that modulate JNK expression in an isoform-specific manner, because, the JNK1 and JNK2 proteins (two isoforms of JNK) "differ by four high conservative amino acid

substitutions (such as Ile Leu and six less conservative and conservative changes", as taught by Kallunki et al., at page 3001, paragraph 1. One of ordinary skill in the art would have been motivated to devise a method of treating a cell proliferative disorder associated with JNK and had a reasonable expectation of success since Karin et al. taught a method of treating a cell proliferative disorder associated with JNK comprising administering to a subject with the disorder a therapeutically effective amount of reagent which modulates JNK.

Claims 1, 14, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Derijard et al. (Cell, 1994 Vol. 76:1025-1037), in view of Karin et al. [WO 95/03324] and Milligan et al. (Journal of Medicinal Chemistry, 1993. 36:1923-1937).

Claims 1 and 18 are drawn to oligonucleotides comprising 8 to 30 nucleotides wherein said nucleotide consists of a sequence specifically hybridizable to a nucleic acid encoding a JNK protein and specifically hybridizable under the condition of modulating the expression of said JNK protein, and where the JNK protein is that of a mammal. Claim 14 is drawn to a method of modulating the expression of JNK cells in cells comprising contacting said cells with the oligonucleotide of claim 1 and claim 16 is drawn to methods of employing the oligonucleotide of the invention for modulating phosphorylation in cells in culture and in animals.

Derijard et al. at page 1026, Figure 1, teach a nucleotide sequence which is a cDNA encoding a JNK protein. Derijard et al., teach that JNK protein, (also known as c-Jun NH_2-terminal kinase), phosphorylates the oncogene c-Jun (see page 1025, paragraph 3) and thereby modulates the oncogenic activity of c-Jun (see page 1031, paragraph 2).

Derijard et al. do not teach an antisense oligonucleotide comprising 8 to 30 nucleotides wherein said nucleotide consists of a sequence specifically hybridizable to a nucleic acid encoding a JNK protein and specifically hybridizable under the condition of modulating the

expression of said JNK protein in vitro or a method of modulating the expression of JNK cells in cells comprising contacting said cells with said antisense oligonucleotide.

Karin et al., teach that "[t]he polynucleotide sequence for JNK also includes sequences complementary to the polynucleotide encoding JNK (antisense sequences). . . The antisense nucleic acids interfere with the translation of the mRNA since the cell will not translate a mRNA that is double-stranded. Antisense oligomers of about 15 nucleotides are preferred, since they are easily synthesized and are less likely to cause problems than larger molecules when introduced into the target JNK-producing cell. The use of antisense methods to inhibit the translation of genes is well known in the art . . . ." Karin at page 16, line 15 to page 17, line 2. Therefore Karin et al. teach a prophetic antisense oligonucleotide comprising 15 nucleotides wherein said nucleotide consists of a sequence specifically hybridizable to a nucleic acid encoding a JNK protein and specifically hybridizable under the condition of modulating the expression of said JNK protein in vitro. Karin et al. also teach a method of modulating the expression of JNK cells in cells comprising contacting said cells with said antisense oligonucleotide. Karin et al., at page 23, line 10 to page 24, line 2, teaches that diseases to be treated by administration of antisense oligonucleotides specific for JNK protein include malignancies, such as cancer of the "lung, breast, lymphoid, gastrointestinal, and genito-urinary tract as well as adenocarcinomas which include malignancies such as most colon cancers, renal-cell carcinoma, prostate cancer, non-small cell carcinoma of the lung, cancer of the small intestine and cancer of the esophagus" and "non-malignant or immunological-related cell-proliferative diseases such as psoriasis, pemphigus vulgaris, Behcet's syndrome, acute respiratory distress syndrome (ARDS), ischemic heart disease, post-dialysis syndrome, leukemia,

rheumatoid arthritis, acquired immune deficiency syndrome, vasculitis, septic shock and other types of acute inflammation, and lipid histocytosis."

Milligan et al. teach making an antisense oligonucleotide if the mRNA sequence (or cDNA) is known: "Antisense oligodeoxynucleotides (ODNs) have been proposed as a major class of new pharmaceuticals. In general, antisense refers to the use of small, synthetic oligonucleotides, resembling single-stranded DNA, to inhibit gene expression [references omitted]. Gene expression is inhibited through hybridization to coding (sense) sequences in a specific messenger RNA (mRNA) target by Watson-Crick base pairing in which adenosine and thymidine or guanosine and cytosine interact through hydrogen bonding (Figure 1). These simple base-pairing rules govern the interaction between the antisense ODNs and the cellular RNA, allowing the design of ODNs to target any gene of a known sequence" (see page 1923).

It would have been obvious at the time the invention was made to one of ordinary skill in the art to make a 15-mer antisense oligonucleotide that targeted a JNK protein-encoding nucleic acid, that modulated expression of said protein and a method for the modulation of expression of said JNK protein, as suggested by Karin et al., using the nucleotide sequence coding for a JNK protein, as taught by Derijard et al. One of ordinary skill in the art would have been motivated to make said antisense oligonucleotide for the nucleotide sequence coding for the JNK for therapeutic administration, as taught by Karin et al., at page 25, lines 6-7 for the purpose of "treating a cell proliferative disorder associated with JNK" by modulating the kinase activity of the JNK protein (Karin et al., page 23, lines 9-12). One of ordinary skill in the art also would have been motivated to use methods employing the oligonucleotide of the invention to modulate the expression of JNK protein in cells and to modulated phosphorylation in cultured cells in

order to study the phosphorylation of oncogenes by the JNK protein, as suggested by the references of Derijard et al. and Karin et al.

One of ordinary skill in the art would have had a reasonable expectation of success to make antisense oligonucleotide sequences complementary to the gene encoding the JNK protein, as taught by Karin et al., that would bind to the mRNA coding for said JNK protein, and so modulate the expression of the JNK protein, and the phosphorylation by JNK protein in cells in culture, because the reference of Derijard et al. teaches the sequence of the gene encoding JNK protein and Milligan et al. teaches that antisense oligonucleotides, in theory, may be designed for gene whose sequence is known.

Claims 2-9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Derijard et al., Karin et al. and Milligan et al., as taken together and applied to claims 1, 14, 16 and 18 above, and further in view of Shibahara et al. and Kallunki et al.

Claims 2-8 and 19 are drawn to the antisense oligonucleotide of claim 1 wherein: At least one of the covalent linkages is modified; at least one of the nucleotides has a modified nucleobase; at least one of the nucleotides has a modified sugar moiety; at least one of the covalent linkages is modified and at least one of the nucleotides has a modified sugar moiety; at least two n-n-contiguous nucleotides have modified sugar moieties; at least two non-contiguous nucleotides have modified sugar moieties and at least of one the covalent linkages is modified; and at least one lipophilic moiety which enhances cellular uptake of the oligonucleotide and wherein the modified nucleobase is 5-methylcytosine, respectively. Claim 9 is drawn to an oligonucleotide comprising from 8-30 nucleotides connected by covalent linkages, wherein said oligonucleotide has a sequence specifically hybridizable with a nucleic acid encoding a first isoform of a JNK protein and is not specifically hybridizable with a nucleic acid encoding a

second isoform of the JNK protein, so that the oligonucleotide modulates the expression of the first isoform of the JNK protein but does not modulate the expression of the second isoform of the JNK proteins.

Derijard et al., Karin et al. and Milligan et al., taken together as above, teach oligonucleotide comprising 8 to 30 nucleotides wherein said nucleotide consists of a sequence specifically hybridizable to a nucleic acid encoding a JNK protein and specifically hybridizable under the condition of modulating the expression of said JNK protein.

Derijard et al., Karin et al. and Milligan et al., taken together as above, do not teach the antisense oligonucleotide wherein: At least one of the covalent linkages is modified; at least one of the nucleotides has a modified nucleobase; at least one of the nucleotides has a modified sugar moiety; at least one of the covalent linkages is modified and at least one of the nucleotides has a modified sugar moiety; at least two non-contiguous nucleotides have modified sugar moieties; at least two non-contiguous nucleotides have modified sugar moieties and at least of one the covalent linkages is modified; and at least one lipophilic moiety which enhances cellular uptake of the oligonucleotide and wherein the modified nucleobase is 5-methylcytosine, respectively. Derijard et al., Karin et al. and Milligan et al., taken together as above do not teach an antisense oligonucleotide which has a sequence specifically hybridizable with a nucleic acid encoding a first isoform of a JNK protein and is not specifically hybridizable with a nucleic acid encoding a second isoform of the JNK protein, so that the oligonucleotide modulates the expression of the first isoform of the JNK protein but does not modulate the expression of the second isoform of the JNK proteins.

Milligan et al., teach at least one modified covalent linkage, (see page 1931-32), as in claim 2; at least one of the nucleotides with a modified nucleobase, (see page 1933), as in claim

3; at least one of the nucleotides has a modified sugar moiety, (see page 1931-32), as in claim 4; and at least one lipophilic moiety which enhances the cellular uptake of the oligonucleotide, (see page 1933, paragraph 4), as in claim 8. Milligan et al. at page 1933, paragraph 2 teaches oligonucleotides comprising 5-methylcytosine.

Shibahara et al. teach at least two non-contiguous nucleotides having modified sugar moieties, (see page 245, Figure 1), as in claim 6; and at least two "non-contiguous" nucleotides having modified sugar moieties and at least one the modified covalent linkages, (see Figure 1), as in claim 7.

Kallunki et al. teach a nucleic acid encoding a first isoform of a JNK protein and which is not identical to a second isoform of the JNK protein, because of "a small region located next to the catalytic pocket of the [JNK] enzyme.

It would have been obvious at the time the invention was made to one of ordinary skill in the art to make the antisense oligonucleotide of claim 1, as taught by Seimiya et al., with the modified covalent linkages, nucleobases, sugar moieties and lipophilic moieties, as taught by Milligan et al.; and with at least two non-contiguous nucleotides having modified sugar moieties and at least one modified covalent linkages, as taught by Shibahara et al. Furthermore, it would have been obvious at the time the invention was made to one of ordinary skill in the art to make antisense oligonucleotides, as taught by Seimiya et al., with the different nucleotide sequences encoding separate JNK isoforms, as taught by Kallunki et al., in order to produce an antisense oligonucleotide which has a sequence specifically hybridizable with a nucleic acid encoding a first isoform of a JNK protein and is not specifically hybridizable with a nucleic acid encoding a second isoform of the JNK protein, so that the oligonucleotide modulates the expression of the

first isoform of the JNK protein but does not modulate the expression of the second isoform of the JNK proteins.

One of ordinary skill in the art also would have been motivated to make said modified oligonucleotide, in order to enhance stability, affinity, and cellular uptake, as taught by the aforementioned prior art. Milligan et al., teach that modifications of the covalent linkage has been shown to impart stability and allow for enhanced affinity and increased cellular permeation of oligonucleotides, (see page 1931, paragraph 2); modification of the nucleobase "offers the opportunity to enhance the affinity" of the oligonucleotide, (Milligan et al., at page 1933, paragraph 2); modification of the sugar moiety "have also been used to enhance stability and affinity", (see page 1932, paragraph 7); and conjugation to a lipophilic moiety "[e]nhanced cellular association", (see 1933, paragraph 4). Furthermore, one of ordinary skill in the art also would have been motivated to make antisense oligonucleotide that target specific JNK isoforms because the isoform "JNK2 displays considerably higher affinity toward c-Jun than JNK1 does", as taught by Kallunki et al., at page 2997, paragraph 1. Kallunki et al. teach that the difference between the affinity of JNK isoforms appears to be due to said amino acid substitutions and "[c]onsistent with this difference, overexpression of wild-type JNK2 but not JNK1 potentiates expression of a c-Jun-dependent reporter gene. Therefore, JNK2 is likely to be responsible for c-Jun activation, whereas JNK1 may be involved in regulation of other substrates." Kallunki et al., at page 2997, paragraph 1. Thus one of ordinary skill in the art would have been motivated to differentiate between the inhibition of expression of JNK2, which has a much higher affinity for the potential oncogene c-Jun, and JNK1, which might regulate other substrates that were part of the normal functioning of the cell, in order to minimize untoward side-effects of, for example, antisense cancer therapy.

One of ordinary skill in the art would have had a reasonable expectation of success of making antisense oligonucleotides that target mammalian JNK-encoding nucleotide sequences, as taught by Seimiya et al., with the oligonucleotide modifications as taught by the reference of Milligan et al. and Shibahara et al., because oligonucleotide modifications would depend upon oligonucleotide chemistry, which would be essentially the same for any oligonucleotide, and would not depend upon the genetic information of the nucleotide sequences, which would vary from gene to gene. Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success to make antisense oligonucleotides that modulate JNK expression in an isoform-specific manner, because, the JNK1 and JNK2 proteins (two isoforms of JNK) "differ by four high conservative amino acid substitutions (such as Ile Leu and six less conservative and conservative changes", as taught by Kallunki et al., at page 3001, paragraph 1.

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
July 29, 2002

SEAN McGARRY
PRIMARY EXAMINER